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METHODS

Effect of Calcium-Binding Additives on Ventricular Fibrillation and Repolarization Changes During Coronary Angiography

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Ventricular fibrillation during coronary angiography with Renografin-76 (meglumine sodium diatrizoate) has been attributed to the calcium-binding additives sodium citrate and sodium ethylenediaminetetraacetic acid (EDTA), which may produce repolarization changes manifested as prolongation of the QT interval. Angiovist-370 is a newer form of meglumine sodium diatrizoate that contains calcium EDTA as its additive and thus has a decreased calcium-binding effect. Eight hundred sixteen patients were prospectively randomized to receive either Renografin-76 or Angiovist-370. Ventricular fibrillation occurred in 10 of 410 patients receiving Renografin-76 and in 0 of 406 patients given Angiovist-370 ($p < 0.0005$).

Clinical data were analyzed without knowledge of other data in the 10 patients treated with Renografin-76 who had ventricular fibrillation (Group I), 103 randomly selected patients who also received Renografin-76 but had no ventricular fibrillation (Group II) and 108 randomly selected patients given Angiovist-370 (Group III). Of several variables examined, only the QT interval differentiated patients receiving Renografin-76 and Angiovist-370. The mean corrected QT interval (QT_c interval) before coronary angiography was slightly but not significantly ($p = 0.7$) higher in Group I than in Groups II and III. Ten seconds after the first left coronary artery injection it was more prolonged in Groups I and II (0.552 and 0.561 second, respectively) than in Group III (0.448 second) ($p < 0.00005$). Similarly, 10 seconds after the first right coronary artery injection it was significantly longer in Groups I and II (0.545 and 0.544 second) than in Group III (0.477 second) ($p < 0.00005$). The mean QT_c interval after coronary angiography was slightly more prolonged in Groups I and II (0.469 and 0.455 second) compared with Group III (0.439 second) ($p = 0.06$).

Thus, the substitution of calcium EDTA in contrast agents significantly decreases the incidence of ventricular fibrillation during coronary angiography, perhaps by attenuating the repolarization changes (with resultant QT interval prolongation) induced by contrast agents.

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Ventricular fibrillation during coronary angiography occurs in 0.6 to 1.3% of patients (1–5). It is unclear why some patients develop this potentially life-threatening complication of coronary angiography; however, it has been suggested that ventricular fibrillation during coronary angiography is a result of the electrophysiologic effects of the contrast media (6–13). Specifically, it has been observed that contrast agents cause a prolongation of repolarization (with resultant QT interval prolongation) (13). A proposed factor responsible for these repolarization changes has been the presence of the calcium-binding additives sodium citrate and sodium ethylenediaminetetraacetic acid (EDTA) found in Renografin-76, the most commonly used formulation of meglumine sodium diatrizoate (14). Preclinical studies have found a reduced incidence of ventricular fibrillation during coronary angiography when using either calcium-enriched Renografin-76 (6) or a newer formulation of meglumine sodium diatrizoate, Angiovist-370 (15), which contains calcium EDTA as its additive, and thus has a reduced propensity to bind calcium. The purpose of this investigation was to prospectively determine whether the incidence of ventricular fibrillation during coronary angiography in humans could be reduced with a calcium-enriched contrast agent, and whether that reduced incidence of ventricular fibrillation could be correlated with changes in repolarization as measured by the QT interval.

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Methods

Study patients. Eight hundred sixteen consecutive patients undergoing cardiac catheterization for the diagnosis of coronary artery disease or valvular heart disease at the Hospital of the Medical College of Pennsylvania from March 1984 through the end of March 1985 were randomly assigned to receive either Renografin-76 (Squibb and Sons, Inc.) or Angiovist-370 (Berlex Imaging, Inc.). Approval was granted by the Committee for the Protection of Human Subjects, and informed consent was obtained from all patients. Patients undergoing percutaneous transluminal coronary angioplasty or thrombolytic therapy were excluded from the study. Coronary arteriography was performed in multiple right and left anterior oblique projections, using either the Judkins or Sones technique. Left ventriculography was performed in the 30° right anterior oblique projection. Premedication consisted of oral administration of 50 mg of diphenhydramine hydrochloride and either 10 mg of diazepam or 50 mg of pentobarbital.

Data collection. Standard 6 lead electrocardiograms were recorded using an Electronics for Medicine or Honeywell Meddars paper recorder at 25 to 100 mm/s paper speed. Electrocardiograms were obtained before the catheterization, up to 10 seconds after the first left and right coronary artery injections and within 5 minutes of completion of the catheterization.

Clinical characteristics, heart rate and QT intervals were obtained for all 10 patients who had ventricular fibrillation during coronary angiography (Group I). Similar variables were measured in every fourth patient selected at random for subgroup analysis. This included 103 patients receiving Renografin-76 (Group II) and 108 patients studied with Angiovist-370 (Group III).

QT intervals from each electrocardiogram were measured by one of three investigators who did not know which contrast agent was used. T wave termination was taken as the transection of the baseline with a line parallel to the rapidly descending portion of the T wave; U waves were excluded. The longest QT interval in any standard lead was used and corrected for heart rate by Bazett's formula:

$$QT_c = \frac{QT}{\sqrt{RR}} \text{ (16).}$$

Statistical analysis. Ventricular fibrillation incidence rates were compared using a chi-square analysis. Clinical characteristics, heart rate and QT intervals were analyzed by two factor analysis of variance, followed by simple main effects analysis and Tukey-A post hoc tests. Results were considered significantly different when $p < 0.05$.

Table 1. Clinical Characteristics of 221 Patients

Characteristics	Group I: n = 10 n (%)	Group II: n = 103 n (%)	Group III: n = 108 n (%)
Age* (yr)	61 ± 4	57 ± 1	55 ± 1
Sex			
Male	4 (40)	77 (72)	71 (66)
Female	6 (60)	29 (27)	37 (34)
History of previous MI	4 (40)	50 (47)	9 (9)
History of prior VT/VF	0 (0)	8 (8)	8 (9)
Medications			
Digoxin	1 (10)	8 (8)	7 (7)
Beta-blockers	6 (60)	62 (60)	55 (51)
Calcium-blockers	2 (20)	52 (50)	44 (41)
Diuretics	3 (30)	27 (26)	23 (21)
Type I antiarrhythmic agents	0 (0)	1 (1)	3 (3)
Ejection fraction*	0.60 ± 0.07	0.64 ± 0.02	0.64 ± 0.01
Cardiac catheterization diagnosis			
Coronary artery disease	7 (70)	75 (73)	70 (65)
One vessel	2 (20)	20 (19)	22 (20)
Two vessel	2 (20)	19 (18)	20 (19)
Three vessel	2 (20)	27 (27)	20 (19)
Left main	1 (10)	9 (9)	8 (7)
Valvular heart disease	0	5 (5)	2 (2)
Other (ASD, HCM)	0	0	2 (2)

*Mean ± standard error of the mean. Group I = ventricular fibrillation after Renographin-76; Group II = no ventricular fibrillation after Renographin-76; Group III = Angiovist-370. ASD = atrial septal defect; HCM = hypertrophic cardiomyopathy; MI = myocardial infarction; VT/VF = ventricular tachycardia/ventricular fibrillation.

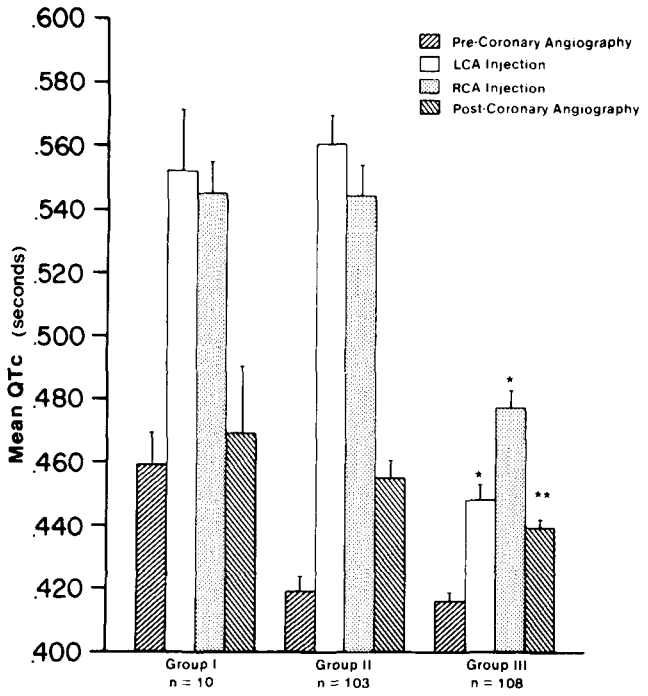

Figure 1. Mean QT_c interval in patients in Group I (patients receiving Renografin-76 who had ventricular fibrillation), Group II (patients receiving Renografin-76 who did not have ventricular fibrillation) and Group III (patients receiving Angiovist-370) before, during and after coronary angiography. LCA = left coronary artery; RCA = right coronary artery. *p <.00005, compared with Groups I and II; **p = 0.06, compared with Groups I and II.

Results

Incidence of ventricular fibrillation. Of the 410 patients randomly assigned to receive Renografin-76, 10 patients (2.4%) had ventricular fibrillation, all of whom survived this event with no adverse aftereffects. Ventricular fibrillation occurred in four patients after right coronary artery injection and in six patients after left coronary artery injection. There were no episodes of ventricular fibrillation in the 406 patients who received Angiovist-370 ($p < 0.0005$).

Clinical features. Clinical characteristics of the 10 patients given Renografin-76 who had ventricular fibrillation (Group I), as well as 103 randomly selected patients receiving Renografin-76 with no ventricular fibrillation (Group II) and 108 patients given Angiovist-370 (Group III) are shown in Table 1. There were no significant differences among the groups with respect to age, sex, history of previous myocardial infarction, history of prior ventricular tachycardia or ventricular fibrillation, or current medications. A very small percentage of patients were taking type I antiarrhythmic drugs, and none were taking type III antiarrhythmic agents. The groups were also similar with regard to severity of coronary artery disease and left ventricular function. Serum potassium in Groups I, II and III was 4.1 ± 0.1, 4.2 ± 0.04 and 4.1 ± 0.04 mEq/liter, respectively.

QT intervals. The mean QT_c interval ± SEM within each group is shown in Figure 1. Before coronary angiography the QT_c interval was longer in Group I than in Groups II and III, but this difference did not reach statistical significance ($p = 0.7$). After initial left and right coronary artery injections, there was less marked QT_c prolongation in Group III (Angiovist-370) than in Groups I and II (Renografin-76) ($p < 0.00005$). After angiography the QT_c interval remained somewhat more prolonged in both groups receiving Renografin-76 (Groups I and II) than in patients receiving Angiovist-370 (Group III), at a borderline statistical level ($p = 0.06$). The mean heart rate was not significantly different among the three groups throughout the cardiac catheterization (Table 2).

Discussion

Myocardial effects of contrast agents. Contrast agents used in coronary arteriography are responsible for profound alterations in cardiac function, including changes in heart rate, blood pressure, peripheral resistance, coronary blood flow, myocardial contractility and blood chemistry (17–21). In addition, electrocardiographic changes have been identified, and include QRS and T wave axis shifts, bradycardia and QT interval prolongation with the latter being linked to contrast media-induced ventricular fibrillation (5,22–26). These changes in repolarization, as reflected by QT_c prolongation, may contribute to an increased incidence of ventricular fibrillation by producing an increased dispersion of repolarization (27). Murdock et al. (13) postulated that with a decrease in QT_c prolongation there is a resultant decrease in conduction delay of premature ventricular beats, and

Table 2. Mean Heart Rates*

	Group I (n = 10)	Group II (n = 103)	Group III (n = 108)
Before coronary angiography	71.6 ± 6	69.4 ± 1.3	69.3 ± 1.2
Left coronary artery injection	86.6 ± 8	69.2 ± 1.4	69.7 ± 1.3
Right coronary artery injection	75.4 ± 8	69.3 ± 1.3	71.4 ± 1.6
After coronary angiography	77.9 ± 5	75.5 ± 1.3	75.3 ± 1.2

*Beats/min ± standard error of the mean. Patient groups defined in Table 1.

therefore sufficient delay to achieve reentry is no longer possible.

Initial attempts to decrease the incidence of ventricular fibrillation during coronary angiography focused on the sodium content of contrast agents. A series of experiments (11,18,28–30) identified an ideal concentration of sodium; a lower concentration resulted in prolonged depolarization and a higher concentration in prolonged repolarization, both of which produced an increased incidence of ventricular fibrillation.

Role of calcium. Calcium flux has also been investigated for its role in the genesis of ventricular fibrillation. Caulfield et al. (31) observed a decrease in ionized serum calcium levels in blood collected from the coronary sinus immediately after coronary artery injection of Renografin-76. They attributed the decrease of the ionized calcium to the chelating action of sodium citrate and sodium EDTA, which are contained in Renografin-76 as stabilizing agents. This finding was further supported by Thomson et al. (6), who demonstrated a lower incidence of ventricular fibrillation in dogs given a calcium-enriched formulation rather than the standard formulation of Renografin-76. More recently, a decreased incidence of ventricular fibrillation in dogs was shown (15) using a newer formulation of meglumine sodium diatrizoate, Angiovist-370, that contains as its additive calcium EDTA, which has less calcium-binding activity than the additives found in Renografin-76. In addition, Murdock et al. (15) found less QT interval prolongation with Angiovist-370 than with Renografin-76. In the only prospective study performed in humans, Wolf and Hirschfeld (14) examined the changes in QT intervals in four patients receiving either Renografin-76 or Hypaque-76 (Winthrop Laboratories), a contrast agent similar to Angiovist-370, which also contains calcium EDTA as its additive. They found less QT interval prolongation with Hypaque-76 and suggested that contrast agents with reduced calcium-binding properties may produce less ventricular fibrillation during coronary angiography. Their study was limited by inclusion of a very small number of patients.

Present study. We prospectively examined the role of calcium-binding additives on ventricular fibrillation during coronary angiography in 816 patients. Several clinical and electrocardiographic characteristics were also analyzed in a randomly selected subset of those patients. We found a marked reduction in the incidence of ventricular fibrillation when using Angiovist-370 (calcium EDTA as additive) as compared with Renografin-76 (sodium citrate and sodium EDTA as additives). Patients receiving Angiovist-370 had significantly less QT interval prolongation during coronary artery injections as compared with patients receiving Renografin-76. These results indicate that the incidence of ventricular fibrillation during coronary angiography, as well as QT_c prolongation (14), can be reduced by eliminating the calcium-binding additives found in contrast agents.

Our study also suggests that baseline repolarization abnormalities may contribute to the incidence of ventricular fibrillation. The QT interval before coronary angiography was higher in Group I (ventricular fibrillation) than in Groups II and III (Renografin-76 and Angiovist-370 without ventricular fibrillation). While this difference is not statistically significant, it supports previously published data (32) in a larger group of patients with ventricular fibrillation in whom QT interval prolongation before angiography was found to be an important risk factor for the development of ventricular fibrillation.

Study limitations. Our study is limited by the fact that comparisons were made between patients with ventricular fibrillation (Group I) and a random sample of the patients receiving Renografin-76 (Group II) and Angiovist-370 (Group III) who were arrhythmia free. This limitation is mitigated by the apparent similarity of the three groups with respect to clinical characteristics and extent of coronary disease. An additional limitation is that QT interval measurements are subject to interobserver and intraobserver variations (33). Our study provided for a blinded analysis of the data, which partially obviates that bias. Nonionic contrast agents were not evaluated in our study, but they also reduce the incidence of ventricular fibrillation when compared with ionic contrast agents (8,9,17). Calcium-enriched forms of meglumine sodium diatrizoate, which are comparably priced with similar contrast media using sodium EDTA as their additive, appear to be more reasonable alternative contrast agents in view of their markedly reduced incidence of ventricular fibrillation. Finally other factors, such as quantity of contrast agent used with each coronary injection, as well as changes in conduction and automaticity, were not analyzed but may be as important as repolarization abnormalities in the genesis of ventricular fibrillation during coronary angiography.

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